UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,384	04/27/2005	Monica Bequet Romero	976-19 PCT/US	3767

7590 07/10/2007

Ronald J Baron
Hoffmann & Baron
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
07/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,384	ROMERO ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-97* is/are pending in the application.

4a) Of the above claim(s) *1-26,28-34 and 36-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to comply*.

Notice to Comply	Application No. 10/571,384	Applicant(s)	
	Examiner Phuong N. Huynh	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

DETAILED ACTION

1. Claims 1-97 are pending.

2. Applicant's election without traverse of Group 22 (claims 27 and 35) in the reply filed on April 10, 2007 is acknowledged.

3. Claims 1-26, 28-34 and 36-97 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 27 and 35, drawn to an immunogenic composition comprising a VEGFR2 or fragments thereof and a mutant of VEGF, administered in the presence of or incorporated into Neisseria meningitidis outer membrane derived VSSP, are being acted upon in this Office Action.

5. Claim 27 is objected to because the term the term "administered in the presence or not" is improper because claim 27 is a product claim and not a method claim. If the composition includes a pharmaceutical acceptable adjuvant, then it is suggested that the term "and" be used.

6. Claim 35 is objected to because it is not clear term "VSSP" stands for. While abbreviation can be used in a claim; to avoid potential confusion, the first recitation of the abbreviation should be preceded by the full terminology. Further, the term "administered in the presence of or incorporated into" is improper because claim 35 is a product claim and not a method claim. If the composition includes Neisseria meningitidis outer membrane derived VSSP, then it is suggested that the term "and" be used. With respect to "incorporated into", it is not clear what is being incorporated into Neisseria meningitidis outer membrane derived VSSP.

7. The disclosure is objected to under 37 CFR 1.821 through 1.825 for failure to supply a sequence identifier to all disclosed sequences. In particular, the sequences in Table 1 and 2 at pages 18-19 lack sequence identifiers. These particular sequences are not present in the paper copy and computer readable copy of sequence listing. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must provide a substitute computer readable form (CFR) copy of the sequence listing, a substitute paper copy of the sequence listing,

as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same, and where applicable, include no new matter, as required by 37 CFR 1.82(e-f) or 1.825(b) or 1.825(d).

8. The disclosure is objected to because of the following informalities:

(1) The run one sentence "Recently, two receptors **where** identified for VEGF named NRP1 and NRP2" at page 6, line 4 should be "were identified".

(2) Improper idiomatic English "US 5788985 **y** 6149921" at pate 9, line 5 and "US 5286484 **y** EP 0474313" at page 8, line 37 should have been "and".

(3) The sentence "These polypeptides **can also be produced fused to proteins with acknowledged** adjuvant activity like p64K..." needs to be revised in proper idiomatic English in compliance with 37 CFR 1.52(a) and (b).

(4) The "SEQ ID1 and SEQ ID2" at page 20, line 8 should have been "SEQ ID NO: 1 and SEQ ID NO: 2".

(5) The "SEQ ID3 and SEQ ID4" at page 20, line 23 should have been "SEQ ID NO: 3 and SEQ ID NO: 4".

(6) The "SEQ ID5 and SEQ ID6" at page 20, line 25 should have been "SEQ ID NO: 5 and SEQ ID NO: 6".

(7) The "SEQ ID7 and SEQ ID8" at page 20, line 28 should have been "SEQ ID NO: 7 and SEQ ID NO: 8".

(8) The "SEQ ID9 and SEQ ID10" on page 21 line 10 should have been "SEQ ID NO: 9 and SEQ ID NO: 10",

(9) The "SEQ ID11 and SEQ ID12" at page 21, line 18 should have been "SEQ ID NO: 11 and SEQ ID NO: 12".

(10) "SEQ ID13 and SEQ ID14" at page 21, line 23 should have been "SEQ ID NO: 13 and SEQ ID NO: 14".

(11) The term "the advantage of inducing **endogen** production of antibodies" at page 15, line 10 should have been "endogenous". Appropriate correction is required.

9. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on pages 15, line 30 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database.

10. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 27 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an immunogenic composition comprising an isolated VEGF-A polypeptide or a VEGF-A peptide selected from the group consisting of the ones shown in Table 1, column 1 at page 18 and an isolated VEGFR-2 polypeptide or a VEGFR-2 peptide selected from the group consisting of the ones shown in Table 2 column 2 at page 19 of the specification, (2) The said immunogenic composition further comprises a pharmaceutically acceptable adjuvant and wherein the adjuvant is *Neisseria meningitidis* outer membrane derived very small particle (VSSP), and (3) The said immunogenic composition wherein the isolated VEGF-A polypeptide or the VEGF-A peptide, and the isolated VEGFR-2 polypeptide or the VEGFR-2 peptide are incorporated into *Neisseria meningitidis* outer derived very small particle (VSSP) for use as an immunogenic composition for inducing the production of antibodies and VEGF and VEGFR-2 specific cytotoxic CD8+ lymphocytes, **does not** reasonably provide enablement for any immunogenic composition comprising any VEGFR2 fragments and any mutant of any VEGF polypeptide as set forth in claim 35 and any immunogenic composition comprising any VEGF and any VEGFR-2 fragments for use as an immunogen for inducing the production of antibodies and VEGF and VEGFR-2 specific cytotoxic CD8+ lymphocytes to treat cancer. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Enablement is not commensurate in scope with claims as how to make and use any and all VEGF "mutant" in combination with any VEGFR-2 fragment other than the specific ones shown in Table 2, col. 2 for inducing VEGF and VEGFR-2 specific antibody and cytotoxic CD8+ lymphocytes.

The specification discloses only an immunogenic composition comprising an isolated VEGF-A polypeptide or a VEGF-A peptide selected from the group consisting of the ones shown in Table 1, column 1 at page 18 and an isolated VEGFR-2 polypeptide or a VEGFR-2 peptide selected from the group consisting of the ones shown in Table 2 column 2 at page 19 of the specification. The immunogenic composition further comprises a pharmaceutically acceptable adjuvant and wherein the adjuvant is *Neisseria menigitidis* outer membrane derived very small particle. The said immunogenic composition wherein the isolated VEGF-A polypeptide or the VEGF-A peptide, and the isolated VEGFR-2 polypeptide or the VEGFR-2 peptides are incorporated into *Neisseria meningitidis* outer derived very small particle (VSSP). The intended use of the claimed immunogenic composition is for inducing VEGF and VEGFR-2 specific antibody and CTL *in vivo*, in turn, for treating cancer.

The specification does not teach how to make and use any "mutant" of any VEGF in combination with any and all VEGFR2 fragments for an immunogenic composition that intended to treat cancer. The "VEGF mutant" without the amino acid sequence has no structure, much less function.

Stryer et al (in Biochemistry, Third edition, W H Freeman Company, New York, pages 31-33, 1998; PTO 892) teach that a protein is highly dependent on the overall structure of the

protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo et al teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495; PTO 892). It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein.

With respect to cytotoxic T cell recognition, Leggatt et al (J Immunology 161: 4728-4735, 1998; PTO 892) teach cytotoxic T cell recognition of a short peptide in the context of a particular MHC class I molecule, and two amino acid substitutions (or pair wise substitution) within a T cell epitope may give results not predictable from the effects of each substitution taken singly (see entire document, abstract, in particular).

With respect to antibody binding, Kobrin et al (J Immunology 146: 2017-2020, 1991; PTO 892) teach that even a single amino acid substitution from aspartic acid to asparagine at residue 95 of the heavy chain variable region of a phosphocholine binding monoclonal antibody resulted in loss of antigen binding (see entire document, abstract, in particular).

Given the numerous VEGF mutant, there is a lack of guidance as to which amino acids within the full length sequence of which VEGF could be mutated such as substitution, deletion, addition and/or combination thereof such that the resulting VEGF mutant still elicits VEGF specific antibody, let alone eliciting VEGF specific CD8+ cytotoxic T cell *in vivo*. Further, there is a lack of *in vivo* working example showing any immunogenic composition comprising any VEGF mutant and any VEGFR-2 fragments or full length VEGFR-2 could elicit antibody to self VEGF and self VEGFR-2 (KDR/Flk-1) as well as VEGF and VEGFR-2 specific CD8 cytotoxic T cells, in turn, effective as a tumor vaccine. Accordingly, it is unpredictable which VEGF mutants in combination with VEGFR-2 and VEGFR-2 fragments thereof in the claimed immunogenic composition are effective for treating cancer.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

13. Claims 27 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any "mutant" of any VEGF for the claimed immunogenic composition, any VEGF fragment other than the VEGF-A fragments as shown in Table 1, col. 1, and any VEGFR-2 fragment other than the ones shown in Table 2, col. 2 for the claimed immunogenic composition that induce VEGF-A specific antibody and VEGF-A specific CTL immune response in vivo to treat cancer.

The specification discloses only an immunogenic composition comprising an isolated VEGF-A polypeptide or a VEGF-A peptide selected from the group consisting of the ones shown in Table 1, column 1 at page 18 and an isolated VEGFR-2 polypeptide or a VEGFR-2 peptide selected from the group consisting of the ones shown in Table 2 column 2 at page 19 of the specification. The immunogenic composition further comprises a pharmaceutically acceptable adjuvant and wherein the adjuvant is *Neisseria meningitidis* outer membrane derived very small particle. The said immunogenic composition wherein the isolated VEGF-A polypeptide or the VEGF-A peptide, and the isolated VEGFR-2 polypeptide or the VEGFR-2 peptides are incorporated into *Neisseria meningitidis* outer derived very small particle (VSSP). The intended use of the claimed immunogenic composition is for inducing VEGF and VEGFR-2 specific antibody and CTL *in vivo*, in turn, for treating cancer.

With the exception of the specific full length VEGF-A polypeptide or the VEGF-A peptides such as the ones shown in Table 1 and the full-length VEGFR-2 (KDR/Flk1) or the specific VEGFR2 peptides such as the ones shown in Table 2 for the claimed composition, there is insufficient written description about the structure associated with function of any and all VEGF mutant, VEGFR-2 polypeptides, VEGFR-2 fragments thereof without the amino acid sequence. The specification as filed does not adequate describe the structure of any and all VEGF mutant, much less such VEGF mutant in combination with any VEGFR-2 or any

fragments of any VEGFR-2 is effective as an immunogenic composition for eliciting VEGF specific antibody and VEGF specific CD8 CTL response, in turn, useful for treating any cancer. The specification does not disclose which amino acids within the full length sequence of all VEGF can be substituted, deleted, added and/or combination thereof such that the VEGF mutant still elicit VEGF-A specific antibody and VEGF-A CD8 cytotoxic T cells for treating cancer.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.). As discussed above, the skilled artisan cannot envision the detail chemical structure of the encompassed genus of VEGF mutant polypeptide in combination with all VEGFR-2 and fragments thereof, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only the full length VEGFR-2 and VEGF-A, the specific VEGFR-2 fragment (shown in Table 2, col. 2) and the specific VEGF-A fragment (shown in Table 1 col. 1) but not the VEGF mutant, VEGFR-2 fragment and VEGF fragment thereof meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

For these reasons, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of VEGF mutant to describe the genus for the claimed immunogenic composition. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 27 is rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/45018 (published September 1999; PTO 892).

The WO 99/45018 publication teaches an immunogenic composition for active immunization against angiogenesis associated antigens wherein the reference composition comprising immunogens such as vascular endothelial growth factor (VEGF) or antigenic fragment thereof and KDR/flk-1 (VEGFR2) and antigenic fragment thereof in the presence of a pharmaceutically acceptable adjuvant (see page 8, second full paragraph, page 11, last paragraph, page 16, last paragraph, in particular). The reference KDR/Flk-1 receptors are also known as VEGFR-2. The reference immunogens may be presented to the immune system by incorporated on the surface of recombinant bacterial cell such as Mycobacterium bovis (BCG), see paragraph bridging pages 17-18, or adsorbed onto adjuvant particles such as aluminum oxide or bacterial adjuvant BCG know in the art (see page 19, in particular). Thus, the reference teachings anticipate the claimed invention.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/45018 (published September 1999; PTO 892) in view of US Pat No 6,149,921 (issued Nov 2000; PTO 892).

The WO 99/45018 publication teaches an immunogenic composition for active immunization against angiogenesis associated antigens wherein the reference composition comprising immunogens such as vascular endothelial growth factor (VEGF) or antigenic fragment thereof (or peptidomemetics which are mutant of VEGF) and KDR/flk-1 (VEGFR2) and antigenic fragments thereof combined with a pharmaceutically acceptable adjuvant (see page 8, second and third full paragraphs, page 11, last paragraph, page 16, last paragraph, in particular). The reference KDR/Flk-1 receptors are also known as VEGFR-2. The reference immunogens may be presented to the immune system by incorporated on the surface of recombinant bacterial cell such as Mycobacterium bovis (BCG), see paragraph bridging pages 17-18, or adsorbed onto adjuvant particles such as aluminum oxide or bacterial adjuvant BCG know in the art (see page 19, in particular).

The invention in claim 35 differs from the teachings of the reference only in that immunogenic composition comprising VEGFR-2 polypeptide or fragments thereof and a mutant of VEGF polypeptide (immunogenic fragment) in the presence of or incorporated into Neisseria meningitidis outer membrane derived very small particles (VSSP) instead of adjuvant particles such as aluminum oxide or bacterial adjuvant BCG know in the art.

The '921 patent teaches very small particle from the outer membrane complex of *N meningitides* as adjuvant for an immunogenic composition to elicit an immunogenic response against self-antigens (see summary, col. 5, lines 21, in particular). The reference immunogen can be dispersed in or incorporated into the outer membrane of *N meningitidis* using ultrasonic bath (see col. 5, lines 8-13, in particular) or other means (see col. 5, lines 14-21, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute adjuvant particles such as aluminum oxide or bacterial adjuvant BCG in the immunogenic composition of the WO 99/45018 publication for the adjuvant such as very small particle from the outer membrane complex of *N meningitides* as taught by the '921 patent.

One having ordinary skill in the art would have been motivated to do this because the '921 patent teaches very small particle from the outer membrane of *Neisseria meningitidis* is useful as an adjuvant to elicit an immunogenic response against self antigens for treating cancer (see summary, col. 5, lines 21, in particular). From the combined teachings of the references, it is

apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Patent Examiner
Technology Center 1600
July 6, 2007